View Online / Journal Homepage / Table of Contents for this issue
Dynamic Article Links

Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4029

www.rsc.org/obc

PAPER

Enantioselective direct aldol reaction of α-keto esters catalyzed by (S_a)-binam-D-prolinamide under quasi solvent-free conditions†‡

Santiago F. Viózquez,[a] Abraham Bañón-Caballero,[a] Gabriela Guillena,*[a] Carmen Nájera*[a] and Enrique Gómez-Bengoa*[b]

Received 31st January 2012, Accepted 22nd March 2012
DOI: 10.1039/c2ob25224d

Published on 23 March 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25224D
Downloaded by Beijing University on 16 June 2012

(S_a)-Binam-D-prolinamide (20 mol%), instead of (S_a)-binam-L-prolinamide, in combination with chloroacetic acid (100 mol%) is an efficient organocatalyst for the direct aldol reaction between α-keto esters as electrophiles and alkyl and α-functionalised ketones, under quasi solvent-free conditions, providing access to highly functionalised chiral quaternary γ-keto α-hydroxyesters with up to 92% ee.

Introduction

The use of organocatalysed protocols in the enantioselective direct aldol reaction is well recognised nowadays due to the practical advantages of these compared to other bio- or metal catalysed procedures.[1] The level of expertise gained in these types of reactions has promoted the application of organocatalysed methods to other enantioselective C–C[2] and C–heteroatom processes.[3] While the organocatalysed aldol reaction with aldehydes as electrophiles is well established, the use of ketones as acceptors has rarely been reported, probably due to the poor electrophilic character of these compounds. Only a few reports using highly active non-enolizable ketones as electrophiles are found in the literature. This reaction has been mainly performed using proline[4] and proline derivatives.[5] In this transformation, very interesting chiral tertiary alcohols,[6] which are key pharmaceutical intermediates,[4b] are formed. In most cases, the use of a large excess of the nucleophilic ketone counterpart is required in order to shift the equilibrium involved to the formation of the corresponding aldol products, diminishing the atom efficiency of the reaction[7] and hampering the general use of this type of transformation. The application of solvent-free reaction conditions[8] to perform the organocatalysed direct aldol by several groups[9] including ours[10–13] has allowed reduction of the excess of the aldol donor and facilitated the use of valuable ketones as starting materials to perform this transformation. The use of prolinamides derived from 1,1′-binaphthyl-2,2′-diamine (binam) **1**[10,14] and **2**[11] (Fig. 1), or even using polystyrene supported binam-prolinamide **3**[12] for the inter-[10,14] and intramolecular[11] aldol reactions under these reaction conditions, has allowed the synthesis of interesting chiral compounds[9e,11c,d] in high levels of enantioselectivity. In all these cases, the best results, for the aldol reaction between aldehydes and ketones or the cross aldol reaction between aldehydes, in terms of diastereo- and enantioselectivities were achieved by using catalyst **1a** [(S_a)-binam-L-prolinamide] or **2** [*N*-tosyl-(S_a)-binam-L-prolinamide].

Only recently the use of solvent-free reaction conditions for the aldol reaction between acetone and α-keto esters using as organocatalyst a primary–tertiary diamine derived from L-serine has been reported.[15] However, chiral prolinamides have been not used for this type of transformation.[1e] Therefore, continuing with our work, we describe here the application of binam-prolinamides in the aldol reaction between α-keto esters and ketones to

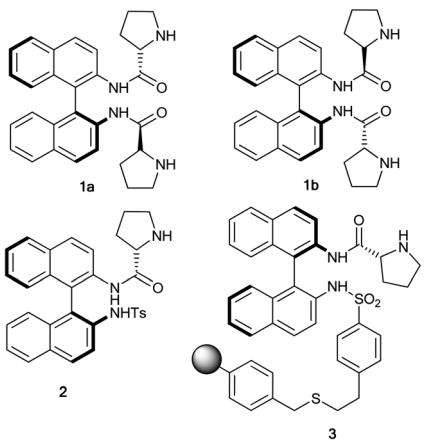


Fig. 1 Binam-prolinamides used as organocatalyst in the aldol reaction.

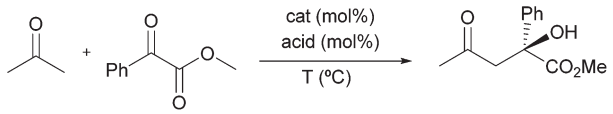
[a]*Dpto. Química Orgánica and Instituto de Síntesis Orgánica, Universidad de Alicante, Apdo. 99, E-03080 Alicante, Spain. E-mail: gabriela.guillena@ua.es, cnajera@ua.es; Fax: +34-965903549; Tel: +34-965903549*
[b]*Departamento de Química Orgánica I, Universidad del País Vasco, Apdo.1072, 20080 San Sebastián, Spain. E-mail: enrique.gomez@ehu.es; Fax: (+) 34-943015270*

† Dedicated to the memory of Prof. Balbino Mancheño.

‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob25224d

View Online

Table 1 Optimization of the reaction conditions between acetone (**4a**) and 2-phenyl-2-oxoacetate (**5a**)[a]



4a **5a** **6aa**

Entry	Cat.	Acid (mol%)	Solvent (mL)	*T* (°C)	*t* (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	AcOH (150)	Acetone (0.5)	25	17	90	16 (*R*)
2	**1a**	AcOH (150)	—	25	17	90	15 (*R*)
3	**1a**	AcOH (20)	—	25	17	93	4 (*R*)
4	**1a**	AcOH (150)	—	0	24	95	32 (*R*)
5	***ent*-1a**	AcOH (150)	—	0	24	98	36 (*S*)
6	**1b**	AcOH (150)	—	0	48	96	56 (*S*)
7	**2**	AcOH (150)	—	0	48	75	0
8	**1b**	AcOH (150)	—	−20	48	95	56 (*S*)
9	**1b**	AcOH (100)	—	0	48	90	60 (*S*)
10	**1b**	AcOH (300)	—	0	48	90	60 (*S*)
11	**1b**	AcOH (100)	H_2O (0.125)	0	96	50	42 (*S*)
12	**1b**	AcOH (100)	Hexane (0.125)	0	48	50	64 (*S*)
13	**1b**	AcOH (100)	CH_2Cl_2 (0.125)	0	96	80	62 (*S*)
14	**1b**	AcOH (100)	THF (0.125)	0	96	75	32 (*S*)
15	**1b**	AcOH (100)	MeOH (0.125)	0	96	40	20 (*S*)
16	**1b**	AcOH (100)	—	25	30	84	16 (*S*)
17	**1b**	Me_3CCO_2H (100)	—	25	30	95	0
18	**1b**	ICH_2CO_2H (100)	—	25	30	97	60 (*S*)
19	**1b**	$ClCH_2CO_2H$ (100)	—	25	30	95	62 (*S*)
20	**1b**	$BrCH_2CO_2H$ (100)	—	25	30	98	50 (*S*)
21	**1b**	Cl_2CHCO_2H (100)	—	25	30	40	30 (*S*)
22	**1b**	CF_3CO_2H (100)	—	25	30	40	16 (*S*)
23	**1b**	$ClCH_2CO_2H$ (100)	—	0	72	82	70 (*S*)
24[d]	**1b**	$ClCH_2CO_2H$ (100)	—	0	72	10	46 (*S*)
25[e]	**1b**	$ClCH_2CO_2H$ (100)	—	0	72	38	60 (*S*)
26[f]	**1b**	$ClCH_2CO_2H$ (100)	—	0	72	15	44 (*S*)

[a] The reaction was carried out using 5 equiv. of acetone (otherwise stated), 20 mol% of catalyst, the indicated amount of acid as co-catalyst at the indicated temperature. [b] Isolated yield after column chromatography. [c] Determined by HPLC. [d] 1 equiv. of ketone was used. [e] 10% of catalyst **1b** was used. [f] 5% of catalyst **1b** was used.

Published on 23 March 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25224D
Downloaded by Beijing University on 16 June 2012

give the corresponding chiral tertiary alcohols. The scope of this reaction would be extended to the use of enolizable α-functionalized ketones, which as far as we know, have not been used before as nucleophile for this type of transformations.

Results and discussion

The reaction between acetone (**4a**) and methyl 2-oxo-2-phenylacetate (**5a**) as α-keto ester and catalyst **1a** (Table 1) was selected as a model for the optimization of the reaction conditions. As it has been reported that the addition of acetic acid allowed the efficient synthesis of aldols **6** using prolinamides as catalysts,[5f] this acid was used as additive and its required amount was studied in this optimization.

Thus, 20 mol% of catalyst **1a** and 150 mol% of acetic acid were used to promote the reaction at 25 °C. The convenience or not of the use of a solvent was evaluated by carrying the reaction using acetone as solvent and nucleophile (Table 1, entry 1) or using only 5 equiv. of acetone in the absence of solvent (Table 1, entry 2). Decreasing the amount of acid co-catalyst led to a drop in the achieved enantioselectivity (Table 1, entry 3). As the yield and enantioselectivity were not affected by the presence of an excess of acetone, the catalytic activities of the organocatalysts **1** and **2** were tested in the absence of solvent (Table 1, entries 4–8). Decreasing the temperature to 0 °C raised the enantioselectivity up to 36% by using catalyst (S_a)-binam-L-prolinamide **1a** (Table 1, entry 4), but the best enantioselectivity (56% ee) was encountered, surprisingly, using the diastereomeric compound (S_a)-binam-D-prolinamide **1b** (Table 1, entry 6). Remarkably, under the same reaction conditions, catalyst *N*-tosyl-(S_a)-binam-L-prolinamide **2** led to the formation of the product **6aa** in lower yields and in racemic form (Table 1, entry 7). Therefore, catalyst **1b** was chosen to optimize the rest of the reaction conditions. Further decrease of the temperature to −20 °C did not improve the results (Table 1, entry 8). Also decreasing or increasing the amount of acid co-catalyst led only to a slight increase of the enantioselectivities (Table 1, entries 9 and 10). The need for a stoichiometric amount of acid as co-catalyst is probably due to the activation of the α-keto ester as electrophile through hydrogen bonding between the two oxygen atoms. The effect of the use of a small amount of solvent was evaluated, finding that the use of non-polar solvents such as hexane or dichloromethane gave better enantioselectivities than the use of a polar solvent such as methanol (Table 1, compare entries 11 to 15) with an increase in the reaction time needed for the reaction completion being observed in all cases.

Finally, the use of other acids as co-catalysts in this transformation was tested. When a weaker acid such as pivalic acid

 This journal is © The Royal Society of Chemistry 2012

View Online

Published on 23 March 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25224D
Downloaded by Beijing University on 16 June 2012

(pK_a = 5.05) was used, the product was obtained in racemic form (Table 1, compare entries 16 and 17). Stronger acids such as iodoacetic acid (pK_a = 3.12) or chloroacetic acid (pK_a = 2.87) gave better enantioselectivities compared to acetic acid under the same reaction conditions (Table 1, entries 18 and 19) with a drop in the enantioselectivities being observed by using acids of lower pK_a such as bromoacetic acid (pK_a = 2.69, Table 1, entry 20), dichloroacetic acid (pK_a = 1.29, Table 1, entry 21) or trifluoroacetic acid (pK_a = 0.23, Table 1, entry 22). After these optimization studies, the best results were those achieved using catalyst **1b** (20 mol%) and chloroacetic acid (100 mol%) as co-catalyst at 0 °C in the absence of solvent, giving product **6aa** in 82% yield and 70% ee (Table 1, entry 23). Under these reaction conditions, the reduction of the amount of ketone or the decrease of catalyst loadings to 10 or 5 mol% led to poorer conversions and lower enantioselectivities (Table 1, entries 24–26).

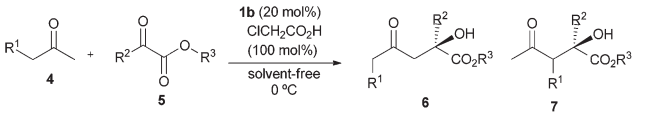
Once the best reaction conditions were established, these were applied in the reaction of several aromatic and heteroaromatic α-keto esters with acetone (Table 2). The substitution of the alkoxy group in the α-keto esters has no influence in the results with methyl 2-oxo-2-phenylacetate or ethyl 2-oxo-2-phenylacetate providing the corresponding products in high yields and moderate enantioselectivities (Table 2, entries 1 and 2). However, the use of an alkyl α-ketoester such as ethyl pyruvate (**5c**) as electrophile led a drop in the enantioselectivity to 23% ee (Table 2, entry 3). The use of an activated α-keto ester such as ethyl 2-(4-nitrophenyl)-2-oxoacetate (**5d**) gave the corresponding product **6ad** in shorter reaction time with excellent yields and improved enantioselectivity (Table 2, entry 4).

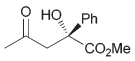
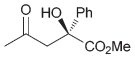
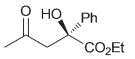
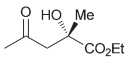
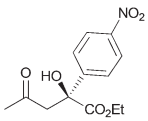
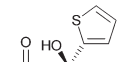
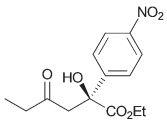
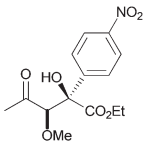
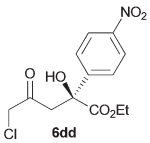
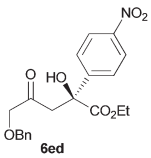
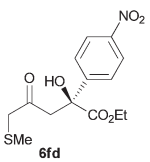
The use of a heteroaromatic α-keto ester was also possible giving product **6ae** in good yield and 54% ee (Table 2, entry 5). Ethyl 2-(4-nitrophenyl)-2-oxoacetate (**5d**) was chosen as the electrophile to study the scope of the reaction with different ketones including α-functionalized ones. These transformations are more challenging due to the need to control the regio-, diastereo- and enantioselectivity. For these nucleophiles longer reaction times were generally required. With the exception of α-methoxyacetone (**4c**), the major isolated products were the iso-isomers **6**, probably due to the steric hindrance around the tertiary alcohol. The yields obtained were highly dependent on the reactivity of the nucleophile.

Thus, butanone (**4b**), α-methoxyacetone (**4c**) and α-benzyloxyacetone (**4e**) gave high yields (Table 2, entries 7, 8 and 10) while less reactive α-chloroacetone (**4d**) and α-methylsulfanylacetone (**4e**) gave lower yields (Table 1, entries 9 and 11). Also, except for the case of ketone **4c**, the enantioselectivities achieved were around 70%. The use of α-methoxyacetone (**4c**) as nucleophile led to the formation of mainly the *anti*-**7cd** isomers in a high enantioselectivity (92% ee, Table 1, entry 8).

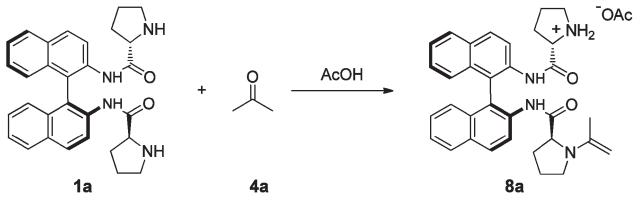
In an attempt to understand the formation of opposite enantiomers with catalysts **1a** (*R*) and **1b** (*S*), the better enantioperformance of catalyst **1b** over catalyst **1a**, and to get some insights regarding the H-bonding network responsible for the catalytic activity, we set out to study the reaction computationally.[16] We assumed that the reaction proceeds first by formation of an enamine between the catalyst and acetone **4a**, which upon protonation with the acetic acid additive would render the quaternary ammonium acetate salt **8a** (or **8b** from **1b**) (Scheme 1).

Table 2 Solvent-free aldol reaction between ketones and α-keto esters[a]



Entry	Major product	*t* (h)	Yield[b] (%)	**6**/**7**[c]	dr[c]	ee[d] (%)
1	 *ent*-**6aa**	24	95	—	—	38[e]
2	 **6aa**	84	84	—	—	69
3	 **6ab**	75	90	—	—	68
4	 **6ac**	17	90	—	—	22
5	 **6ad**	18	92	—	—	71
6	 **6ae**	72	93	—	—	54
7	 **6bd**	26	89	9 : 1	1 : 1	68
8	 **7cd**	72	96	1 : 9	9 : 1	92
9	 **6dd**	96	60	99 : 1	—	73
10	 **6ed**	72	85	4 : 1	9 : 1	64
11	 **6fd**	85	20	99 : 1	—	76

[a] Reaction conditions: ketone **4** (5 equiv.), α-keto ester **5**, **1b** (20 mol%), $ClCH_2CO_2H$ (100 mol%), 0 °C. [b] Isolated yield after column chromatography. [c] For the *anti*/*syn*-isomer determined by ^1H NMR of crude product. [d] Determined by HPLC (major isomer). [e] Catalyst **1a** (20 mol%) was used.



Scheme 1 Formation of the enamine intermediate **8a**.

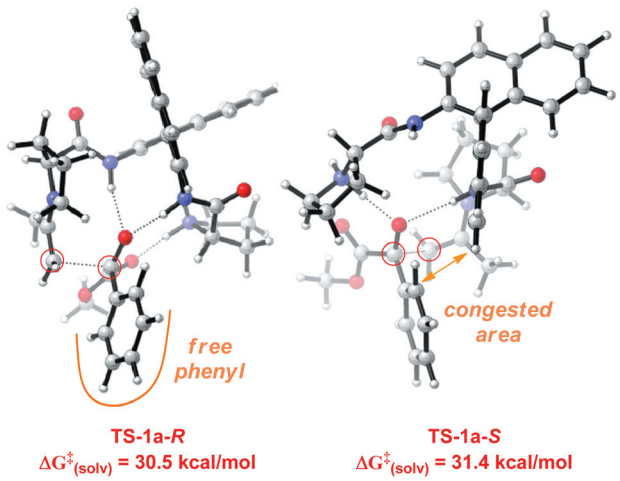


Fig. 2 Transition state for the reaction with the catalyst **1a**. Red-circled atoms are those involved in the C–C bond formation.

We computed the reaction between **8a** or **8b** with keto ester **5a** through the *Re* and *Si* faces of the electrophile. In each case, several transition states with different H-bonding patterns were screened and evaluated. The lowest in energy for each enantiomer are shown in Fig. 2 (catalyst **1a**) and Fig. 3 (**1b**). In fair agreement with the experimental results, the former shows a slight preference (Fig. 2, $\Delta\Delta G^{\ddagger}$ = 0.9 kcal mol^{-1}) for the formation of the *R* enantiomer, and a larger preference for the *S* enantiomer is seen in the latter (Fig. 3, $\Delta\Delta G^{\ddagger}$ = 1.5 kcal mol^{-1}). These values account for a theoretical 4 : 1 *R*-selectivity with **1a**, and 12 : 1 *S*-selectivity with **1b**.

Interestingly, the H-bond network does not differ substantially in each pair of diastereomeric transition states. In both **TS-1a-*R*** and **TS-1a-*S***, the reactive carbonyl oxygen of the keto ester is activated by two H-bonds with two of the NH groups within the catalyst (Fig. 2). Seemingly, in both **TS-1b-*R*** and **TS-1b-*S***, a single activation takes place with the amidic NH group. All these NH-bonds present similar length, 1.9 Å in the case of **TS-1b-*R*** and **TS-1b-*S*** (Fig. 3). Thus, the selectivity is not related to the H-bond activation pattern, and must have a different origin.

In fact, we found that the position of the phenyl ring of **5a** during the transition states is an important factor that might explain the *R*/*S* selectivity. As shown in Fig. 2, there is considerable steric hindrance between the phenyl group and the binaphthyl portion of the catalyst in the *S*-TS, whereas in *R*-TS the phenyl group points outwards, and is better positioned in a fairly free area. The opposite is true for **1b** in Fig. 3; the phenyl ring is positioned in the less sterically demanding area in the *S*-TS, and in the more congested one in *R*-TS.[17]

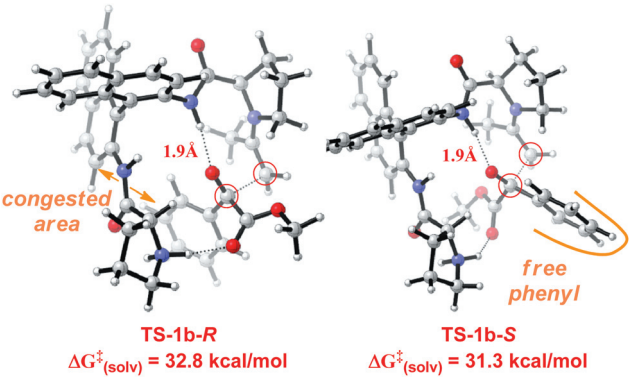


Fig. 3 Transition state for the reaction with the catalyst **1b**.

Conclusions

The use of nearly solvent free conditions has been applied in the aldol reaction between α-keto esters and ketones, including functionalized ones catalysed by binam-prolinamides using chloroacetic acid as catalyst. The highly functionalized corresponding tertiary alcohols have been achieved in good yields and regioselectivities with enantioselectivities up to 92% ee, when (S_a)-binam-D-prolinamide instead of (S_a)-binam-L-prolinamide was used as catalyst. DFT computational studies indicate that steric effects between the phenyl-keto ester **5a** and the binaphthyl portion of the bulky catalyst dictate the stereoselectivity.

Experimental section

General

Catalysts were prepared following the previously described procedures.[10b,11c,12] Dry DMF, dry toluene, dry CH_2Cl_2, piperidine and triethylamine and all other reagents were commercially available and used without further purification. Only the structurally most important peaks of the IR spectra (recorded on a Nicolet Impact 400D) are listed. ^{1}H NMR (300 MHz, 400 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker AC-300 using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HPLC analyses were performed on a Agilent 1100 series equipped with a chiral column (detailed for each compound below), using mixtures of n-hexane/isopropyl alcohol (IPA) as mobile phase, at 25 °C. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots were visualised under UV light (λ = 254 nm). For flash chromatography we employed Merck silica gel 60 (0.063–0.2 mm). Elemental analysis was carried out in the Research Technical Services of the University of Alicante.

General procedure for the solvent-free aldol reaction catalysed by 1b

To a mixture of the corresponding α-keto ester **5** (0.25 mmol), catalyst **1b** (0.024 g, 0.05 mmol, 0.2 equiv.) and chloroacetic acid (0.024 g, 0.25 mmol, 1 equiv.) at 0 °C was added the corresponding ketone **4** (1.25 mmol, 5 equiv.). The reaction was

Downloaded by Beijing University on 16 June 2012
Published on 23 March 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25224D

This journal is © The Royal Society of Chemistry 2012

Published on 23 March 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25224D
Downloaded by Beijing University on 16 June 2012

stirred until the α-ketoester was consumed (monitored by TLC). Then, CH_2Cl_2 (0.5 mL) was added to the mixture which was purified by flash chromatography (hexanes–EtOAc) to yield the pure product **6**.

(*S*)-Methyl 2-hydroxy-4-oxo-2-phenylpentanoate (6aa)[15]

White solid; Mp = 56 °C (EtOAc); R_f = 0.35 (hexanes–EtOAc 7 : 3); δ_H (300 MHz; $CDCl_3$, Me_4Si) 2.21 (s, 3H, $CH_3C{=}O$), 3.01 (d, J = 17.6 Hz, 1H, CH_2), 3.56 (d, J = 17.6 Hz, 1H, CH2), 3.76 (s, 3H, CO_2CH_3), 4.43 (s, 1H, OH), 7.28–7.43 (m, 3H), 7.56 (d, J = 8.9 Hz, 2H, ArH); δ_c (75 MHz; $CDCl_3$, Me_4Si) 30.6 ($CH_3C{=}O$), 52.9 (CH_2), 53.1 (CO_2CH_3), 76.3 (C–OH), 124.8 (ArCH), 128.0 (ArCH), 128.4 (ArCH), 140.1 (ArC), 174.3 ($CO_2CH_2CH_3$), 207.8 (C=O); HPLC (Chiralpak AD, n-hexane–i-PrOH: 80 : 20, 0.8 mL min^{-1}), t_R 9.508 (minor), t_R 11.189 (major).

(*S*)-Ethyl 2-hydroxy-4-oxo-2-phenylpentanoate (6ab)[15]

White solid; Mp = 60 °C (EtOAc); R_f = 0.33 (hexanes–EtOAc 7 : 3); δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.20 (s, 3H, $COCH_3$), 3.02 (d, J = 17.6 Hz, 1H, CH_2), 3.55 (d, J = 17.6 Hz, 1H, CH_2), 4.22 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.39 (s, 1H, OH), 7.27–7.41 (m, 3H), 7.51–7.65 (m, 2H, ArH); δ_c (75 MHz; $CDCl_3$, Me_4Si) 13.9 (OCH_2CH_3), 30.6 ($CH_3C{=}O$), 53.0 (CH_2), 62.2 (OCH_2CH_3), 76.5 (C–OH), 124.8 (ArCH), 128.0 (ArCH), 128.4 (ArC), 140.3 (ArC), 173.8 ($CO_2CH_2CH_3$), 207.6 (C=O); HPLC (Chiralcel ODH, n-hexane–i-PrOH: 90 : 10, 0.8 mL min^{-1}), t_R 21.090 (minor), t_R 26.470 (major).

(*S*)-Ethyl 2-hydroxy-2-methyl-4-oxopentanoate (6ac)[18]

Colorless oil; R_f = 0.29 (hexanes–EtOAc 7 : 3); δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.28 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.39 (s, 3H, $CH_3C{=}O$), 2.17 (s, 3H, CH_3COH), 2.81 (d, J = 17.6 Hz, 1H, CH_2), 3.13 (d, J = 17.6 Hz, 1H, CH_2), 3.82 (s, 1H, OH), 4.23 (q, J = 7.1 Hz, 2H, OCH_2CH_3); δ_c (75 MHz; $CDCl_3$, Me_4Si) 14.0 (OCH_2CH_3), 26.1 (CH_3COH), 30.5 ($CH_3C{=}O$), 52.2 (CH_2), 61.7 (OCH_2CH_3), 72.4 (COH), 175.7 ($CO_2CH_2CH_3$), 207.7 (C=O); HPLC (Chiralpak AS, n-hexane–i-PrOH: 98 : 02, 0.6 mL min^{-1}), t_R 23.267 (minor), t_R 29.345 (major).

(*S*)-Ethyl 2-hydroxy-2-(4-nitrophenyl)-4-oxopentanoate (6ad)[18]

White solid; Mp = 67 °C (EtOAc); R_f = 0.35 (hexanes–EtOAc 7 : 3); δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.24 (s, 3H, $CH_3C{=}O$), 3.01 (d, J = 17.6 Hz, 1H, CH2), 3.57 (d, J = 17.6 Hz, 1H, CH_2), 4.25 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.53 (s, 1H, OH), 7.80 (d, J = 8.9 Hz, 2H, ArH), 8.22 (d, J = 8.9 Hz, 2H, ArH); δ_c (75 MHz; $CDCl_3$, Me_4Si) 13.8 (OCH_2CH_3), 30.5 ($CH_3C{=}O$), 52.8 (CH_2), 62.8 (OCH_2CH_3), 76.1 (COH), 123.5 (ArCH), 126.0 (ArCH), 147.2 (Ar), 147.6 (ArC), 172.7 (CO_2), 206.8 (C=O); HPLC (Chiralpak AD, n-hexane–i-PrOH: 90 : 10, 0.6 mL min^{-1}), t_R 21.427 (minor), t_R 23.833 (major).

(*R*)-Ethyl 2-hydroxy-4-oxo-2-(thiophen-2-yl)pentanoate (6ae)[4f]

Colorless oil; R_f = 0.33 (hexanes–EtOAc 7 : 3); δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.28 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.20 (s, 3H, CH_3CO), 3.20 (d, J = 17.6 Hz, 1H, CH_2), 3.51 (d, J = 17.6 Hz, 1H, CH_2), 4.26 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.45 (s, 1H, OH), 6.97 (dd, J = 3.6, 5.1 Hz, 1H, ArH), 7.06 (dd, J = 1.3, 3.6 Hz, 1H, ArH), 7.36–7.22 (m, 1H, ArH).; δ_c (75 MHz; $CDCl_3$, Me_4Si) 13.9 (OCH_2CH_3), 30.5 ($CH_3C{=}O$), 53.6 (CH_2), 62.6 (OCH_2CH_3), 74.8 (COH), 123.7 (ArCH), 125.3 (ArCH), 127.0 (ArCH), 145.1 (ArC), 172.8 (CO_2), 206.2 (C=O); HPLC (Chiralpak AD, n-hexane–i-PrOH: 90 : 10, 0.6 mL min^{-1}), t_R 21.218 (major), t_R 26.330 (minor).

(*S*)-Ethyl 2-hydroxy-2-(4-nitrophenyl)-4-oxohexanoate (6bd)

Yellow solid; Mp = 55 °C (EtOAc); $[\alpha]_D^{25}$ = 47 (c 1.3, $CHCl_3$); R_f = 0.29 (hexanes–EtOAc 7 : 3); IR ν_{max}/cm^{-1} (KBr) 3485, 3112, 2981, 1730, 1605, 1593, 1516, 1403, 1341, 1268, 1109, 855 cm^{-1}; δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.09 (t, J = 7.3 Hz, 3H, $OCCH_2CH_3$), 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.40–2.66 (m, 2H, $OCCH_2CH_3$), 2.99 (d, J = 17.4 Hz, 1H, CH_2), 3.54 (d, J = 17.4 Hz, 1H, CH_2), 4.26 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.60 (s, 1H, OH), 7.81 (d, J = 8.8 Hz, 2H, ArCH), 8.21 (d, J = 8.8 Hz, 2H, ArCH); δ_c (75 MHz; $CDCl_3$, Me_4Si) 7.2 ($O{=}CCH_2CH_3$), 13.8 (OCH_2CH_3), 36.5 (CH_2), 51.6 (CH_2), 63.3 (OCH_2CH_3), 76.2 (C–OH), 123.7 (ArH), 126.3 (ArH), 147.0 (Ar), 147.8 (Ar), 172.4 ($CO_2CH_2CH_3$), 200.3 (C=O) HRMS-DIP (m/z): [M^+ − CO_2Et] calcd for $C_{13}H_{12}NO_4$ 223.1; found: 223.1. HPLC (Chiralcel ODH, n-hexane–i-PrOH: 90 : 10, 0.5 mL min^{-1}), t_R 26.766 (minor), t_R 27.586 (major).

(*R*)-Ethyl 2-hydroxy-3-methoxy-2-(4-nitrophenyl)-4-oxopentanoate (7cd)

Brown oil; $[\alpha]_D^{25}$ = −124 (c 1.17, $CHCl_3$); R_f = 0.30 (hexanes–EtOAc 7 : 3); IR ν_{max}/cm^{-1} (film) 3335, 3192, 2964, 2869, 1676, 1592; δ_H (300 MHz; $CDCl_3$, Me_4Si) 2.15 (s, 3H, $O{=}CCH_3$), 3.46 (s, 3H, OCH_3), 4.20 (s, 1H, OH), 4.26 (s, 1H, $CHOCH_3$), 7.88 (d, J = 9.0 Hz, 2H, ArCH), 8.21 (d, J = 9.0 Hz, 2H, ArCH); δ_c (75 MHz; $CDCl_3$, Me_4Si) 14.1 (OCH_2CH_3), 27.7 ($O{=}CCH_3$), 59.5 (OCH_3), 63.6 (OCH_2CH_3), 80.0 (C–OH), 90.3 ($HCOCH_3$), 123.2 (ArCH), 127.7 (ArCH), 145.1 (ArC), 147.8 (ArC), 171.1 ($CO_2CH_2CH_3$), 209.8 (C=O); HRMS-DIP (m/z): [M^+ − CO_2Et] calcd for $C_{11}H_{12}NO_5$ 238.0; found: 238.2. HPLC (Chiralpak AD, n-hexane–i-PrOH: 90 : 10, 0.5 mL min^{-1}), t_R 59.164 (minor), t_R 31.471 (major).

(*S*)-Ethyl 5-chloro-2-hydroxy-2-(4-nitrophenyl)-4-oxopentanoate (6dd)

Colorless solid; Mp = 95 °C (EtOAc); $[\alpha]_D^{25}$ = −185 (c 1, $CHCl_3$); R_f = 0.29 (hexanes–EtOAc 7 : 3); IR ν_{max}/cm^{-1} (film) 3475, 3108, 3077, 3000, 2939, 1734, 1722, 1686, 1593, 1516, 1403, 1341, 1268, 1101, 859; δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.22 (d, J = 17.4 Hz, 1H, CH_2), 3.43 (s, 3H, OCH_3), 3.63 (d, J = 17.4 Hz, 1H, CH_2), 4.14 (s, 2H, $ClCH_2CO$), 4.29 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.33

(s, 1H, OH), 7.81 (d, J = 9.0 Hz, 2H, ArH), 8.24 (d, J = 9.0 Hz, 2H, ArH); δ_c (75 MHz; $CDCl_3$, Me_4Si) 13.9 (CH_3), 48.3 (CH_2), 49.3 ($ClCH_2$), 62.7 (OCH_2CH_3), 77.1 (C–OH), 123.4 (ArCH), 126.1 (ArCH), 147.4 (ArC), 147.5 (ArC), 172.7 ($CO_2CH_2CH_3$), 209.6 (CO); HRMS-DIP (m/z): [M^+ − CO_2Et] calcd for $C_{10}H_9ClNO_4$ 243.6; found 243.1; HPLC (Chiralpak AD, n-hexane–i-PrOH: 90 : 10, 1.0 mL min^{-1}), t_R 21.344 (minor), t_R 31.130 (major).

(*S*)-Ethyl 5-(benzyloxy)-2-hydroxy-2-(4-nitrophenyl)-4-oxopentanoate (6ed)

Brown oil; R_f = 0.29 (hexanes–EtOAc 7 : 3); 3 IR ν_{max}/cm^{-1} (film) 3493, 2977, 2921, 2864, 1732, 1603, 1521, 1348, 1258, 1211, 1106; cm^{-1}; δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.27 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.12 (d, J = 17.7 Hz, 1H, CH_2), 3.54 (d, J = 17.7 Hz, 1H, CH_2), 4.09 (s, 2H, O═CCH_2OBn), 4.26 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.40 (s, 1H, OH), 4.59 (s, 2H, OCH_2Ph), 7.29–7.41 (m, 5H, ArH), 7.82 (d, J = 9.0 Hz, 2H, ArH), 8.22 (d, J = 9.0 Hz, 2H, ArH); δ_c (75 MHz; $CDCl_3$, Me_4Si) 13.9 (CH_3), 48.8 (O═CCH_2COH), 63.0 (OCH_2), 73.6 (CH_2Ar), 75.2 (O═CCH_2OBn), 76.0 (HOCAr), 123.6 (ArC), 126.3 (ArC), 128.0 (ArC), 128.2 (ArC), 128.6 (ArC), 136.7 (ArC), 147.4 (ArC), 147.7 (ArC), 172.7 ($CO_2CH_2CH_3$), 206.9 (CO); HRMS-DIP (m/z): [M^+ − CO_2Et] calcd for $C_{17}H_{17}NO_5$ 314.1000; found 314.1034; HPLC (Chiralpak AD, n-hexane–i-PrOH: 90 : 10, 1.0 mL min^{-1}), t_R 32.022 (minor), t_R 46.248 (major).

(*S*)-Ethyl 2-hydroxy-5-(methylthio)-2-(4-nitrophenyl)-4-oxopentanoate (6fd)

Brown oil; $[\alpha]_D^{25}$ = −65 (c 1, $CHCl_3$); R_f = 0.35 (hexanes–EtOAc 7 : 3); IR ν_{max}/cm^{-1} (film) 3485, 3192, 2981, 2920, 1735, 1605, 1522, 1348, 1105, 856; δ_H (300 MHz; $CDCl_3$, Me_4Si) 1.28 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.07 (s, 3H, SCH_3), 3.22 (s, 2H, SCH_3CH_2CO), 3.30 (d, J = 17.5 Hz, 1H, CH_2), 3.72 (d, J = 17.5 Hz, 1H, CH_2), 4.27 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.49 (s, 1H, OH), 7.82 (d, J = 9.0 Hz, 2H, ArH), 8.22 (d, J = 9.0 Hz, 2H, ArH); δ_c (75 MHz; $CDCl_3$, Me_4Si) 13.9 (CH_3), 15.4 (SCH_3), 43.2 (CH_2), 49.3 (CH_2), 62.9 (OCH_2CH_3), 76.1 (C–OH), 123.5 (ArH), 126.3 (ArH), 147.3 (Ar), 147.6 (Ar), 172.7 ($CO_2CH_2CH_3$), 203.2 (C═O); HRMS-DIP (m/z): [M^+] calcd for $C_{13}H_{17}NO_7$ 327.1; found 327.1; HPLC (Chiralpak AD, n-hexane–i-PrOH: 90 : 10, 0.9 mL min^{-1}), t_R 38.943 (minor), t_R 59.684 (major).

Acknowledgements

This research was supported by the Ministerio de Ciencia e Innovación (MICINN: Projects CTQ2007-62771/BQU, CTQ2010-20387, and Consolider Ingenio2010 CSD2007-00006,), FEDER, the Generalitat Valenciana (Project PROMETEO/2009/039), and the EU (ORCA action CM0905). We also thank SGI/IZO-SGIker UPV/EHU for allocation of computational resources. A.B.-C. thanks the Spanish MICINN for a predoctoral fellowship (FPU AP2009-3601).

Notes and references

1 (*a*) *Modern Aldol Reactions*, ed. R. Marhrwald, Wiley-VCH, Weinheim, 2004, vol. 1 and 2; (*b*) G. Guillena, C. Nájera and D. J. Ramón, *Tetrahedron: Asymmetry*, 2007, **18**, 2249–2293; (*c*) L. M. Geary and P. G. Hultin, *Tetrahedron: Asymmetry*, 2009, **20**, 131–173; (*d*) S. G. Zlotin, A. S. Kucherenko and I. P. Beletskaya, *Russ. Chem. Rev.*, 2009, **78**, 737–784; (*e*) B. M. Trost and C. S. Brindle, *Chem. Soc. Rev.*, 2010, **39**, 1600–1632.

2 *Enantioselective Organocatalyzed Reactions*, ed. R. Marhrwald, Springer, 2011, vol. 1 and 2.

3 (*a*) M. Marigo and K. A. Jørgensen, *Chem. Commun.*, 2006, 2001–2011; (*b*) G. Guillena and D. J. Ramón, *Tetrahedron: Asymmetry*, 2006, **17**, 1465–1492; (*c*) G. Guillena and D. J. Ramón, *Curr. Org. Chem.*, 2011, **15**, 296–327.

4 (*a*) L.-H. Qiu, Z.-H. Shen, C.-Q. Shi, Y.-H. Liu and Y.-W. Zhang, *Chin. J. Chem.*, 2005, **23**, 584–588; (*b*) O. Tokuda, T. Kano, W.-G. Gao, T. Ikemoto and K. Maruoka, *Org. Lett.*, 2005, **7**, 5103–5105; (*c*) Y.-J. Wang, Z.-H. Shen, B. Li and Y.-W. Zhang, *Chin. J. Chem.*, 2006, **24**, 1196–1199; (*d*) S. Samanta and C.-G. Zhao, *Tetrahedron Lett.*, 2006, **47**, 3383–3386; (*e*) S. Samanta and C.-G. Zhao, *J. Am. Chem. Soc.*, 2006, **128**, 7442–7443; (*f*) G. London, G. Szöllősi and M. Bartók, *J. Mol. Catal. A: Chem.*, 2007, **267**, 98–101; (*g*) Y. Wang, Z. Shen, B. Li, Y. Zhang and Y. Zhang, *Chem. Commun.*, 2007, 1284–1286; (*h*) J. Yang, T. Wang, Z. Ding, Z. Shen and Y. Zhang, *Org. Biomol. Chem.*, 2009, **7**, 2208–2213; (*i*) S. M. Landge and B. Török, *Catal. Lett.*, 2009, **131**, 432–439.

5 (*a*) P. Dambruoso, A. Massi and A. Dondoni, *Org. Lett.*, 2005, **7**, 4657–4660; (*b*) G. Luppi, P. G. Cozzi, M. Monari, B. Kaptein, Q. B. Broxterman and C. Tomasini, *J. Org. Chem.*, 2005, **70**, 7418–7421; (*c*) Z. Tang, L.-F. Cun, X. Cui, Ai.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *Org. Lett.*, 2006, **8**, 1263–1266; (*d*) G. Luppi, M. Monari, R. J. Corrêa, F. A. Violante, A. C. Pinto, B. Kaptein, Q. B. Broxterman, S. J. Garden and C. Tomasini, *Tetrahedron*, 2006, **62**, 12017–12024; (*e*) X.-Y. Xu, Z. Tang, Y.-Z. Wang, S.-W. Luo, L.-F. Cun and L.-Z. Gong, *J. Org. Chem.*, 2007, **72**, 9905–9913; (*f*) F. Wang, Y. Xiong, X. Liu and X. Feng, *Adv. Synth. Catal.*, 2007, **349**, 2665–2668; (*g*) X.-J. Wang, Y. Zhao and J.-T. Liu, *Org. Lett.*, 2007, **9**, 1343–1345; (*h*) J.-R. Chen, X.-P. Liu, X.-Y. Zhu, L. Li, Y.-F. Qiao, J.-M. Zhang and W.-J. Xiao, *Tetrahedron*, 2007, **63**, 10437–10444; (*i*) X.-J. Wang, Y. Zhao and J.-T. Liu, *Synthesis*, 2008, 3967–3973; (*j*) S. Nakamura, N. Hara, H. Nakashima, K. Kubo, N. Shibata and T. Toru, *Chem.–Eur. J.*, 2008, **14**, 8079–8081; (*k*) D. Zhang and C. Yuan, *Tetrahedron*, 2008, **64**, 2480–2488; (*l*) C. Zheng, Y. Wu, X. Wang and G. Zhao, *Adv. Synth. Catal.*, 2008, **350**, 2690–2694; (*m*) A. M. Bernard, A. Frongia, P. P. Piras, F. Secci and M. Spiga, *Tetrahedron Lett.*, 2008, **49**, 3037–3041; (*n*) J. Jiang, X. Chen, J. Wang, Y. Hui, X. Liu, L. Lin and X. Feng, *Org. Biomol. Chem.*, 2009, **7**, 4355–4357; (*o*) G. Angelici, R. J. Corrêa, S. J. Garden and C. Tomasini, *Tetrahedron Lett.*, 2009, **50**, 814–817.

6 For recent reviews on enantioselective preparation of molecules bearing quaternary stereocenters, see: (*a*) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2004, **43**, 284–287; (*b*) D. J. Ramón and M. Yus, *Curr. Org. Chem.*, 2004, **8**, 149–193; (*c*) D. J. Ramón and M. Yus, in *Quaternary Stereocenters: Challenges for Organic Synthesis*, ed. J. Christoffers and A. Baro, Wiley-VCH, Weinheim, 2005, ch. 7, p. 207; (*d*) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473–1482; (*e*) O. Riant and J. Hannedouche, *Org. Biomol. Chem.*, 2007, **5**, 873–888.

7 (*a*) B. M. Trost, *Science*, 1991, **254**, 1471–1477; (*b*) R. A. Sheldon, *Pure Appl. Chem.*, 2000, **72**, 1233–1246; (*c*) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695–705; (*d*) B. M. Trost, M. U. Frederiksen, U. Mathias and M. T. Rudd, *Angew. Chem., Int. Ed.*, 2005, **44**, 6630–6666; (*e*) G. Guillena, D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2007, **47**, 2358–2364.

8 (*a*) J. O. Metzger, *Angew. Chem., Int. Ed.*, 1998, **37**, 2975–2978; (*b*) K. Tanaka, *Solvent-free Organic Synthesis*, Wiley-VCH, Weinheim, 2003; (*c*) G. Kaupp, *Top. Curr. Chem.*, 2005, 95–184.

9 (*a*) B. Rodríguez, T. Rantanen and C. Bolm, *Angew. Chem., Int. Ed.*, 2006, **45**, 6924–6926; (*b*) Y. Hayashi, S. Aratake, T. Itoh, T. Okano, T. Sumiya and M. Shoji, *Chem. Commun.*, 2007, 957–959; (*c*) B. Rodríguez, A. Bruckmann and C. Bolm, *Chem.–Eur. J.*, 2007, **13**, 4710–4722; (*d*) Y.-C. Teo and P. P.-F. Lee, *Synth. Commun.*, 2009, **39**, 3081–3091; (*e*) C. Worch and C. Bolm, *Synlett*, 2009, 2425–2428; (*f*) B. Bradshaw, G. Etxebarria-Jardí and J. Bonjoch, *J. Am. Chem. Soc.*, 2010, **132**, 5966–5967.

Published on 23 March 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25224D
Downloaded by Beijing University on 16 June 2012

This journal is © The Royal Society of Chemistry 2012

View Online

10 (*a*) G. Guillena, M. C. Hita, C. Nájera and S. F. Viózquez, *Tetrahedron: Asymmetry*, 2007, **18**, 2300–2304; (*b*) G. Guillena, M. C. Hita, C. Nájera and S. F. Viózquez, *J. Org. Chem.*, 2008, **73**, 5933–5943.
11 (*a*) G. Guillena, C. Nájera and S. F. Viózquez, *Synlett*, 2008, 3031–3035; (*b*) B. Bradshaw, G. Etxebarría-Jardi, J. Bonjoch, S. F. Viózquez, G. Guillena and C. Nájera, *Adv. Synth. Catal.*, 2009, **351**, 2482–2490; (*c*) S. F. Viózquez, G. Guillena, C. Nájera, B. Bradshaw, G. Etxebarría-Jardi and J. Bonjoch, *Org. Synth.*, 2011, **88**, 317–329; (*d*) B. Bradshaw, G. Etxebarría-Jardi, J. Bonjoch, S. F. Viózquez, G. Guillena and C. Nájera, *Org. Synth.*, 2011, **88**, 330–341.
12 A. Bañón-Caballero, G. Guillena and C. Nájera, *Green Chem.*, 2010, **12**, 1599–1606.
13 (*a*) D. Almaşi, D. A. Alonso and C. Nájera, *Adv. Synth. Catal.*, 2008, **350**, 2467–2472; (*b*) D. Almaşi, D. A. Alonso, A.-N. Balaguer and C. Nájera, *Adv. Synth. Catal.*, 2009, **351**, 1123–1131.
14 (*a*) G. Guillena, M. C. Hita and C. Nájera, *Tetrahedron: Asymmetry*, 2006, **17**, 729–733; (*b*) D. Gryko, B. Kowalczyk and L. Zawadzki, *Synlett*, 2006, 1059–1062; (*c*) G. Guillena, M. C. Hita and C. Nájera, *Tetrahedron: Asymmetry*, 2006, **17**, 1493–1497. (*corrigendum: Tetrahedron: Asymmetry*, 2007, **18**, 1031); (*d*) G. Guillena, M. C. Hita and C. Nájera, *Tetrahedron: Asymmetry*, 2006, **17**, 1027–1031. (*corrigendum: Tetrahedron: Asymmetry*, 2007, **18**, 1030); (*e*) S. Guizzetti, M. Benaglia, L. Pignataro and A. Puglisi, *Tetrahedron: Asymmetry*, 2006, **17**, 2754–2770; (*f*) G. Guillena, M. C. Hita and C. Nájera, *Tetrahedron: Asymmetry*, 2007, **18**, 1272–1277; (*g*) G.-N. Ma, Y.-P. Zhang and M. Shi, *Synthesis*, 2007, 197–208; (*h*) S. Guizzetti, M. Benaglia, L. Raimondi and G. Celentano, *Org. Lett.*, 2007, **9**, 1247–1250; (*i*) G. Guillena, M. C. Hita and C. Nájera, *ARKIVOC*, 2007, **iv**, 260–269. (corrigendum: *ARKIVOC*, 2007, **i**, 146–147); (*j*) A. S. Kucherenko, D. E. Syutkin and S. G. Zlotin, *Russ. Chem. Bull.*, 2008, **57**, 591–594; (*k*) G. Guillena, C. Nájera, S. F. Viózquez and M. Yus, *ARKIVOC*, 2011, **iii**, 166–178.
15 Z. Jiang and Y. Lu, *Tetrahedron Lett.*, 2010, **51**, 1884–1886.
16 DFT studies were carried out at the B3LYP/6-311+G** level in a solvent model system (iefpcm, solvent = acetone). For further details, see ESI.‡.
17 For a schematic representation of the transition states, see ESI.‡.
18 M. Raj, G. S. Parashari and V. K. Singh, *Adv. Synth. Catal.*, 2009, **351**, 1284–1288.

Published on 23 March 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25224D
Downloaded by Beijing University on 16 June 2012